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Case Report

Annals of Behavioral Neuroscience

Illicit Sympathomimetic Drug Abuse in Demyelinating Diseases

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Abstract

Multiple Sclerosis (MS) is an inflammatory demyelinating disease characterized by progressive motor deficits. Behavioral problems have previously been linked to the use of illicit drugs such as cocaine and amphetamine. We present 4 patients with frequent abuse of illicit sympathomimetics who presented with symptomatic White Matter Lesions (WML). Three patients had positive Oligoclonal Bands (OCB), one patient without OCB revealed marked pleocytosis. In this case-series we present clinical and radiological features and discuss possible mechanisms underlying substance abuse in patients with demyelinating lesions. Previous case reports in illicit sympathomimetic substance abusers highlight leukoencephalopathy rather than focally demyelinating WML. We hypothesize a two hit model with drug abuse exacerbating an unknown underlying diagnosis of MS.

Keywords: Cocaine; Amphetamine; Sympathomimetics; Leukoencephalopathy; White matter lesions; Demyelination; Multiple sclerosis

Abbreviations: WML: White Matter Lesion; ADEM: Acute Disseminated Encephalomyelitis; CIS: Clinically Isolated Syndrome; OCBs: Oligoclonal Bands; MS: Multiple Sclerosis; ADHD: Attention Deficit Hyperactive Disorder

Case Presentation

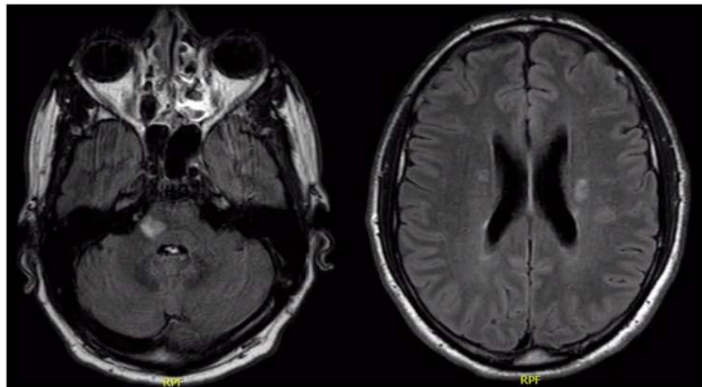
Case 1

A 43 year-old male was admitted to the stroke unit due to slurred speech, right-sided paresthesias and weakness. His prior medical history was positive of type II diabetes. He had a recent admission to the Psychiatric Ward due to suicidal ideation. He admitted to severe cocaine abuse. The neurological exam revealed discrete dysarthria, right-side hyposthesia and weakness. Vital signs, blood draws and ECG were normal. CT brain

with angiography, chest x-ray and carotid ultrasound were normal. The patient recalled, one month prior to admission and at the age of 17, left-sided numbness lasting for weeks. MRI of the brain showed multiple WML including the pons and medulla and Dawson's fingers in the cerebrum. Two lesions of the left corona radiata were contrast-enhancing. Spinal tap showed mild pleocytosis 22 cells (86% polymorphonuclear), elevated glucose and protein, respectively 4,5 and 0,75, positive OCBs and neurofilament-light >10.000. VEP were normal.

At follow up the patient reported complete remission

of his symptoms. Despite an attempt to wean off cocaine he had not been successful and the patient was lost to follow-up.



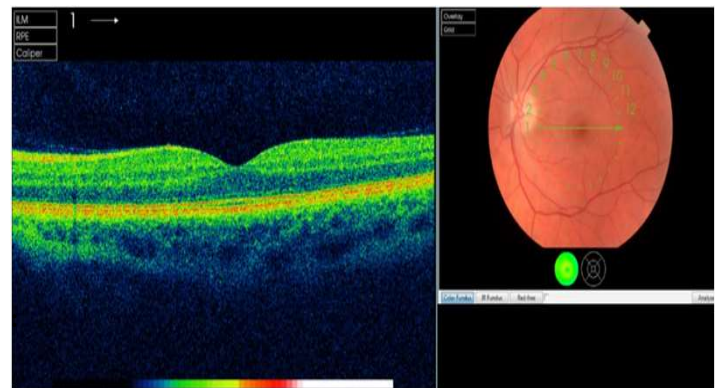
Case 1: MRI pt 1, (FLAIR)

Case 2

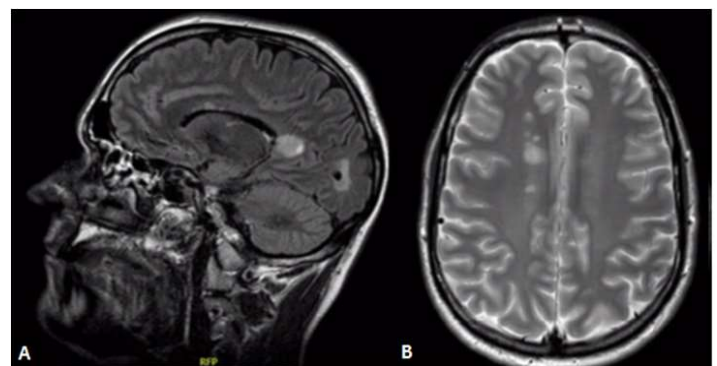
39 year-old male complained of sudden onset of blurry vision on both eyes two weeks prior to admission. His medical history was negative except for previous laser surgery for severe myopia. He claimed light tremor of the hands since childhood. He had consulted an ophthalmologist 2 days after presentation, who found no eye abnormalities or signs of optic neuritis. The visual symptoms progressed, on admission he complained of problems in color vision. On neurological examination, right-sided hyperreflexia, slight ataxia and dysarthric speech was noted. A MRI of the neuroaxis revealed 16 WML fulfilling 3 out of 4 McDonald's criteria. Five lesions were contrast-enhancing and two lesions tumefactive. Optic nerves were normal on MRI. A seasoned neuro-ophthalmologist could not reveal any abnormalities suggestive of optic neuritis. Yet, he reported incomplete remission of his visual problems 4 weeks after presentation. Spinal tap was for positive OCBs. A diagnosis of CIS was made and he started on Teriflunomid. MRI at 3-months follow-up revealed the treatment response with regression of multiple lesions and absence of contrast-enhancement.

One year later he developed a relapse with sudden onset left-sided weakness. CT including angiography showed no signs of ischemia, stenotic changes or vasospasms. Neurological evaluation confirmed left-sided hemiparesis, (lower limb>upper limb), moderate ataxia and unsteady gait, the patient now requiring a walking cane. MRI showed newly tumefactive contrast-enhancing WML. He was refractive to high-dose IV corticosteroids and subsequently treated with plasma-

exchange. A psychiatric consult was debated due to suicidal ideation. Neuropsychological testing revealed cognitive impairment involving psychomotor speed, complex attention and episodic memory. The patient was switched over to Natalizumab and has not suffered any new relapse. A VEP performed 14 months after first presentation, revealed bilateral prolonged latencies supportive of optic nerve abnormalities. In retrospect, the patient admitted to abuse of cocaine and amphetamine including time at first presentation. Visual disturbances appeared shortly after intake and on subsequent episodes of illicit substance abuse.



Case 2: OCT, pt 2 (normal)



MRI, pt 2, at presentation (A = FLAIR, B = T2 + contrast)



MRI, pt 2, at relapse (Both T2 + contrast)

Case 3

A 38 year-old male, who suffered from attention deficit disorder, Tourette's syndrome and recurrent depressions, was admitted due to complaints of right-sided altered sensation, burning pain, problems with coordination, headache and dizziness. His symptoms, however, had been progressive for 6 months. A neurological evaluation found brisk deep tendon reflexes, extensive left plantar response and right-sided hypoaesthesia. Blood works, including infectious panel, were normal. Spinal tap revealed mild pleocytosis 7 and positive OCB, protein and glucose were normal. A MRI of the neuroaxis was performed and revealed one medullary lesion at C3 suggestive of a demyelinating lesion. He admitted to substantial cocaine abuse.

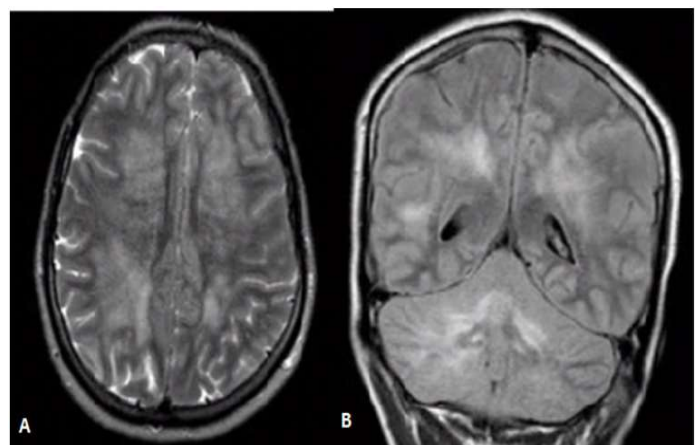


Case 3: MRI pt3, at presentation (T2)

Case 4

A 25 year-old male was admitted to the hospital in a confusional state following several days with severe headache, nausea, vomiting and mild fever. The patient reported recurrent visual problems. The patient presented with decreased level of consciousness. Vital signs and ECG were normal. CT brain including angiography was normal and excluded sinus venous thrombosis. Spinal tap revealed an opening pressure of 25 mm H₂O, mild mononuclear pleocytosis 21 cells and elevated protein of 0.73. Blood work including an extensive infectious panel were normal. Encephalitis was suspected and treatment with acyclovir, ampicillin and dexamethasone was initiated. The patient improved following Spinal tap procedure. MRI revealed non-contrast-enhancing symmetric hyperintensities in the cerebrum, midbrain and cerebellum. Due to the mild episode of fever and

monophasic course, a radiological diagnosis of ADEM was proposed despite lack of contrast-enhancement, and the patient was treated with high-dose IV corticosteroids. The patient improved further and was discharged with no motor or cognitive deficits. MRI 3 weeks after presentation showed regression of the white matter hyperintensities. The patient, however, was re-admitted to the hospital in a confusional state 6 weeks after presentation, again with decreased level of consciousness, vomiting, mild fever and blurred vision. Neurological exam now revealed bilateral ataxia in arms and legs. A Spinal tap revealed marked increase in pleocytosis 159 cells, increased protein 1.63 and positive S-100. Microbial work-up was negative. PET-scans of brain and whole body were negative. The patient improved and demanded to be discharged despite pending work-up. He was readmitted 3 days later with headache, nausea and vomiting. Again, CT angiography was negative and MRI revealed bilateral non-contrast-enhancing symmetric hyperintensities. Renewed Spinal tap, however, revealed improvement in pleocytosis. Although, the patient had denied active substance abuse on previous admissions it now became evident that the patient was actively abusing cocaine, amphetamine and methamphetamine. On the basis of toxic encephalopathy the patient was again treated with high-dose IV corticosteroids, he remarkably improved and was discharged without neurological deficits. The patient had never succeeded to pursue a formal education, accordingly due to psychological problems in school-age. Neuropsychological testing at follow-up was normal. MRI at one month follow-up later showed regression of the hyperintensities. Control Spinal tap revealed normalization of pleocytosis. Of note, all Spinal taps were negative of OCBs.



Case 4: MRI pt4, at presentation (A = T2+contrast, B = FLAIR)

Discussion and Conclusions

Multiple Sclerosis is an inflammatory demyelinating disease and the most common cause of non-traumatic progressive disability in young adults [1]. Cognitive dysfunction is a frequent feature and may correlate to cortical lesions evident at disease onset and progression [2]. Focus on these debilitating features of the disease has increased in the later years, while research in to possible behavioral problems is still scarce. Patients diagnosed with pediatric MS have demonstrated co-morbid psychiatric diagnosis with anxiety disorders, ADHD and mood disorders associated with cognitive impairment [3]. In adult patients diagnosed with MS, more than 14% expressed suicidal ideation such as thoughts of self-harm or being better off dead [4]. Suicidal ideation in MS patients associated with male sex, medical co-morbidity, poor quality of life and being unmarried [4]. Few studies have assessed premorbid risk-behavior in MS prior to MS diagnosis. Hawkes et al. showed risk-behavior association for recreational drug use i.e. cannabis, attending all-night parties, gambling, more sexual partners and termination of one or more pregnancies compared to headache patients [5]. A systematic review and meta-analysis of 23 studies including 1831 participant's, concluded that behavioral problems occur frequently in MS patients [6]. Lability (41%), irritability (38%), inflexibility (26%), aggression (23%), impatience (22%) and apathy (22%) were the most commonly reported behavioral problems. Behavioral problems and substance abuse have long been suggested to have a close link [7]. In a cross-sectional study performed in the U.S. in 1991, 19% of patients admitted to the use of psychoactive drugs [8]. A study by Bombardier et al. found that 7, 8% had used illicit drugs in the past month [9]. Neither elaborated upon the type of drugs most commonly used.

Several studies have highlighted the severity of leukoencephalopathy in cocaine abusers [10-12], and few studies found symptomatic MRI lesions in cocaine users [13-20] and amphetamine users [21,22]. Ryan et al. [20] demonstrated myelin pallor, macrophage infiltration, axonal spheroid formation with relative axonal sparing and amyloid precursor protein deposition (an immunohistochemical marker of acute axonal injury), all histological features which may be consistent with inflammatory demyelination. Of note, no evidence of vasculitis was present in the cases. Weis et al. demonstrated sharply demarcated demyelination, perivascular but not vasculitic inflammation, HLA DR II positive macrophage infiltration, reactive astrogliosis and relative axonal sparing, all features consistent with

inflammatory demyelination [21]. Furthermore, they detected the presence of amphetamine within the demyelinated lesion using gas chromatography and mass spectroscopy. Hook et al. [23] reported a case series with active inflammatory demyelination in brain biopsies from patients receiving 5-fluorouracil and levamisole. Clinically, the patients demonstrated altered mental status changes and ataxia, symptoms resolving after cessation of therapy and administration of high-dose corticosteroids. With regard to cocaine abuse it should be noted that it is still unclear whether the damaging effect causing demyelination is due to cocaine itself or its additive levamisole [14,15,18,24].

The patients in our case series were all men, unmarried had a history of behavioral or psychiatric problems. In retrospect, they admitted to substantial abuse of cocaine and/or amphetamine, only when no other explanation for their signs and symptoms could be resolved. All patients revealed Spinal taps with mild to moderate pleocytosis and 3/4 had positive OCBs highlighting a neuroinflammatory process. One patient followed a relapsing-remitting MS course with symptoms possibly since childhood. Although, careful eye exams could not reveal any abnormalities supporting optic neuritis the patient developed increased optic nerve latencies during the disease course consistent with his relapsing-remitting MS. It seems plausible the tumefactive presentation of WMLs in this patient might be related to illegal substance abuse exacerbating co-existing demyelinating disease. In two patients diagnosed with CIS only, one patient described symptoms suggestive of an undiagnosed demyelinating disease at the age of 17. However, he started cocaine abuse at this age. The patient with CIS restricted to the spinal cord did not reveal any cerebral lesions. Neuropathological studies demonstrate the presence of cortical lesions in MS patients, which may exceed the presence of WML [25,26]. This patient was diagnosed with attention deficit disorder and Tourette, and it may be speculated that these co-morbidities could reflect underlying cortical pathology. It remains unsettled, however, whether his co-morbid psychiatric diagnosis left him prone to illegal substance abuse causing an isolated demyelinating event, or whether the patient had an undiagnosed inflammatory demyelinating disorder exacerbated by the substance abuse. Two patients complained of visual disturbances which could not be determined on examination. Both bilateral optic neuritis [27] and recurrent perineuritis [28] have been described in cocaine abusers. At least in one patient it remains unresolved whether the optic nerve abnormalities at

follow-up were due to MS or due to cocaine abuse.

The use of legal sympathomimetic drugs in MS patients is prescribed to treat non-motor related deficits, and is reported to relieve cognitive symptoms, especially fatigue [29,30]. The degree to which MS patients abuse psychoactive drugs as a mean of self-medicating behavioral and cognitive symptoms is unknown. The patients at time of diagnosis may be reluctant to report the abuse to the caring physician due to the illicit status of the drug. Additionally, the caring physician may not routinely screen for illicit drugs since MS patients commonly are not suspected to exert risk-behavior. Follow-up of MS patients is dominated by motor assessment as a mean to detect disease relapse or progression, behavioral and cognitive symptoms only to a lesser degree.

Our last patient presented with recurrent encephalopathy and markedly increased pleocytosis. In spite the patient having the most severe pleocytosis, all Spinal taps were negative of OCBs and the MR hyperintensities were neither diagnostic of MS nor ADEM, but revealed neuroimaging features previously described in cocaine associated leukoencephalopathy [13,19-21]. It might be possible that sympathomimetic-induced leukoencephalopathy is a disease entity of its own. A monosymptomatic fatal course and radiological features demonstrating symmetric leukoencephalopathy could support this notion [13,16,19-21]. However, the presence of WML fulfilling McDonald criteria with positive OCB suggests CIS or MS. This notion is supported in case reports of recurrent multi-focal leukoencephalopathy [17,18].

In conclusion, CIS and MS may be underestimated in patients with active abuse of sympathomimetic drugs. The finding of positive OCBs and radiological findings fulfilling McDonald criteria support a diagnosis of demyelinating disease despite active substance abuse. Leukoencephalopathy in cocaine and amphetamine abusers may be recurrent and reveal highly inflammatory spinal fluid. Neuroimaging features revealing symmetric leukoencephalopathic changes and the lack of OCBs support toxic encephalopathy despite a relapsing course.

Abuse of sympathomimetics in MS patients may be more widespread than commonly estimated and may relate to self-medication of behavioral and cognitive dysfunction. Neuropathological studies demonstrate inflammatory demyelination in patients abusing sympathomimetic drugs. Tumefactive demyelinating lesions may occur in

MS patients abusing such substances, and may reflect a double-hit of a MS relapse and toxic demyelination. It is reasonable to speculate that an association exists between behavioral problems and illegal substance abuse in MS patients. Studies systematically analyzing the extent and reasons for sympathomimetic drug abuse in MS patients may shed light on the degree of possible self-medicating non-motor deficits. The effect of steroids in patients with possible cocaine induced leukoencephalopathy is still hypothetical [18]. However, when there is doubt as to whether a patient is suffering from a MS attack, or whether the symptoms are based solely on the use of cocaine, it seems, cases reported so far, safe to treat with corticosteroids.

We presented a small case series of patients within the demyelinating spectrum who abused cocaine and/or amphetamine at time of presentation, and further discussed possible interactions of demyelination and illicit sympathomimetics. It remains, unclear whether the patients' demyelinating disease was triggered by the use of illicit substances or whether carrying a diagnosis of demyelinating disease leaves subgroups of MS patients prone to risk-behavior such as substances abuse. In either case, given the fact that illicit sympathomimetic substances may exacerbate an underlying demyelinating disease, the case-reports or discussion presented, highlight the need for awareness of a possible potentiating effect of illicit substance use in MS patients.

Consent

All patients provided informed consent for their cases and accompanying images to be published.

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